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SMALL MOLECULE NITROSAMINES VS. NDSRIs

WHY TESTING APPROACHES DIFFER

FDA's September 2024 revised guidance (Revision 2) clearly distinguishes two structural classes of nitrosamine impurities: small molecule nitrosamines and nitrosamine drug substance-related impurities (NDSRIs).

Factor	Small Molecule Nitrosamines	NDSRIs
What They Are	Relatively common impurities (NDMA, NDEA, NDBA, NMPA)	Share structural similarity to the API
How They Form	Arise from reagents, solvents, recovered materials, or manufacturing components	Vulnerable amine groups in API structure react with nitrosating agents
Where They Occur	Can appear in multiple products	Typically, unique to each drug substance
Analytical Approach	Relatively standardized analytical approaches	Product-specific analytical methods required
Detection Requirements	Parts-per-billion range or lower	Parts-per-billion in complex matrices with API, excipients, and degradation products
Key Challenge	Method optimization	Matrix effects from API/excipients can suppress or enhance ionization; reference standards are unavailable for many NDSRIs
Typical Techniques	LC-HRMS, LC-MS/MS, GC-MS/MS	LC-MS/MS (widely adopted for NDSRI analysis), LC-HRMS
Method Validation Considerations	Standard validation approaches	Often requires matrix-matched calibration, internal standard (if available), or standard addition techniques
Acceptable Intake (AI) Limits	Established limits	FDA has established limits for some NDSRIs; many others require risk-based AI derivation using available mutagenicity and carcinogenicity data

4 Key Technical Considerations for NDSRI Testing

Method Development

Product-specific method development is time-consuming, requiring optimization of extraction, chromatography, and mass spectrometry parameters

Risk Assessment

Risk assessment should evaluate API structure, intermediates, impurities, and degradation products for vulnerable amine groups

Method Validation

Method validation must demonstrate reliable detection in the specific product matrix

Matrix Effects

Matrix effects from API and excipients can affect quantitation accuracy

Element's analytical chemistry laboratories provide NDSRI method development, confirmatory testing, and risk assessment support. Click or scan the QR code to speak with an expert.